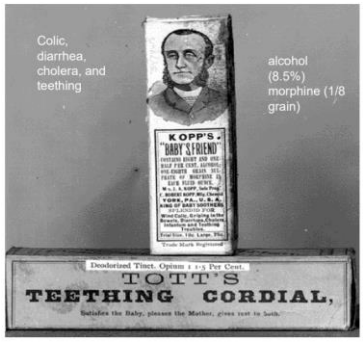
Slide 1	# *Drug Use in Children* **Anna Ponnampalam** **Department of Physiology** **University of Auckland**	**Acknowldegement** **Associate Professor Brian Anderson**
Slide 2	"Paediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but... it has its own independent range and horizon…" Dr Abraham Jacobi 1889	
Slide 3	## Objectives - Understand the major sources of variability affecting the response to medicines in children - Appreciate the relative contributions of body size, body composition, maturation and organ function to variability - Learn the principles of dose individualization based on predictable sources of variability	

Slide 4

Historical Drug Development in Children



Slide 5

Foetal Drug Exposure Adverse Effects

- lithium, carbimazole *Goitre*
- tetracycline *Abnormal teeth/bones*
- NSAIDs *Closure of ductus arteriosus*
- ethanol *Foetal alcohol syndrome*
- nicotine *Low birth weight, increased mortality*
- Methadone *Withdrawal syndrome*

Slide 6

Drug Therapy in Pediatric Patients

- Inadequate research data currently exists for prescribers to ensure safe dosing for infants/children.

  →Two thirds of drugs *used* in pediatrics have never been *tested* in pediatric patients

  - **Best Pharmaceuticals for Children Act (2002)**
  - **Pediatric Research Equity Act of 2003**
- **20 % of drugs were *ineffective* for children** (even though they were effective for adults)
- **30 % of drugs caused unanticipated side effects**, some of which were potentially lethal
- **20 % of drugs required dosages different** from those that had been extrapolated from dosages used in adults
- **These laws were permanently reauthorized as part of the FDA Safety and Innovation Act (FDASIA) of 2012**

Slide 7	**Incidence of Adverse Drug Events** • Medication error rate: pediatric error rates approximately equal to adult error rates • Errors in pediatrics are 3 times more likely to be associated with a potential ADE • Neonatal ICU: patient group with highest error and potential ADE rate • 74% of errors and 79% of potential ADEs occur in ***ordering*** phase Fortescue E, et al. *Pediatrics.* 2003;111(4 pt 1):722–9. Kaushal R, et al. *JAMA*. 2001;285:2114–20.	
Slide 8	**Reasons for Increased Risk** • **Different and changing pharmacokinetic parameters** • Lack of pediatric formulations, dosage forms, guidelines • Calculation errors • Inconsistent measurement of preparations • Problems with drug delivery systems	
Slide 9	**Pediatric and Neonatal Pharmacokinetics** • One size doesn't fit all – Preterm neonates (<36 weeks' gestation) – Full-term neonates (birth to 30 days) – Infants (1–12 months) – Toddlers (1–4 years) – Children (5–12 years) – Adolescents (>12 years)	

Slide 10

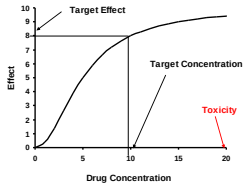
Differences in the young

- **Size**
  - Smaller
    - Distances shorter, faster BMR, faster onset time
- **Maturation**
  - Body composition changing (V) } Pharmacokinetics
  - Drug metabolism immature (CL) } Pharmacokinetics
  - Response to drugs different } Pharmacodynamics
- **Toxicity**
  - Short term (e.g. verapamil and arrest)
  - Long term (e.g. tetracycline and teeth)

Slide 11

What do we want to know to determine dose?

- **Concentration-response relationship (PD)**
- **Target effect**
- **Target concentration**
- **Dose to achieve concentration (PK)**
- **Covariate effects**
  - age, weight, disease
- **Toxicity data**



Slide 12

What do we want to know to determine dose?

- **Concentration-response relationship (PD)**
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- **Dose to achieve concentration (PK)**
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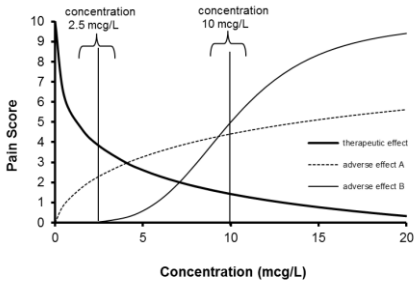
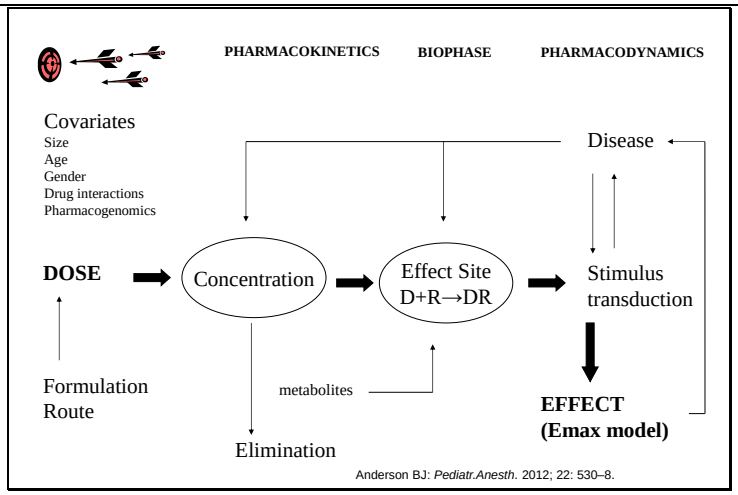


Slide 13



Anderson BJ: *Pediatr.Anesth.* 2012; 22: 530–8.

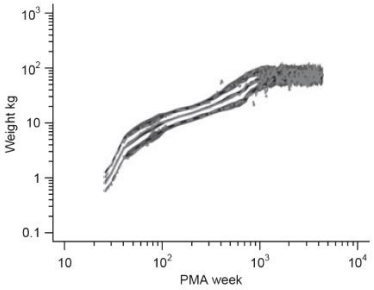
Slide 14

Paediatric Differences

- **Size**
- **Growth & development**
- **Ethics**
  - Autonomy, beneficence, blood loss, min distress
- **Disease spectrum**
  - Bronchiolitis and bronchodilators
- **Potential for future harm**
  - Stilboestrol - *vaginal adenocarcinoma*

Slide 15

Growth



Separation of
Size usually kg
Maturation

Sumpter A. Pediatr Anesth 2011

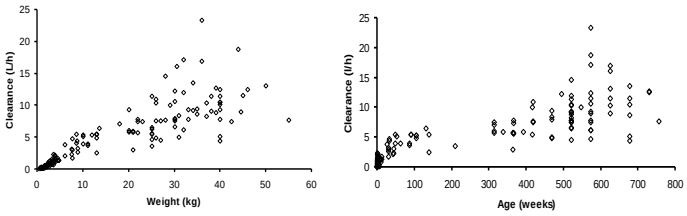
Slide 16

The Major PK Covariates in Children

- **SIZE**
- **Maturation**
- **Organ Function**
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

Slide 17

Paracetamol clearance –weight or age?



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Body size is primary covariate

- **500x weight difference** (e.g. 0.5-250 kg)
- **Parameters expressed as function of size**
- **Common size models**
  - **per kilogram**
    - **Under estimates under 40 kg**
  - **body surface area**
    - **Overestimates under 20 kg**
  - **Allometric**

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Size Models

PER KILOGRAM MODEL

BODY SURFACE AREA MODEL

ALLOMETRIC MODEL

Slide 20

Per Kilogram Model

- **Under predicts dose if weight < 47 kg**
- **Error increases as size decreases**
- **Explanations for under prediction fallacious**
  - **Morphine – relative big liver**
  - **Fentanyl – increased hepatic blood flow**
  - **Remifentanil - ???**

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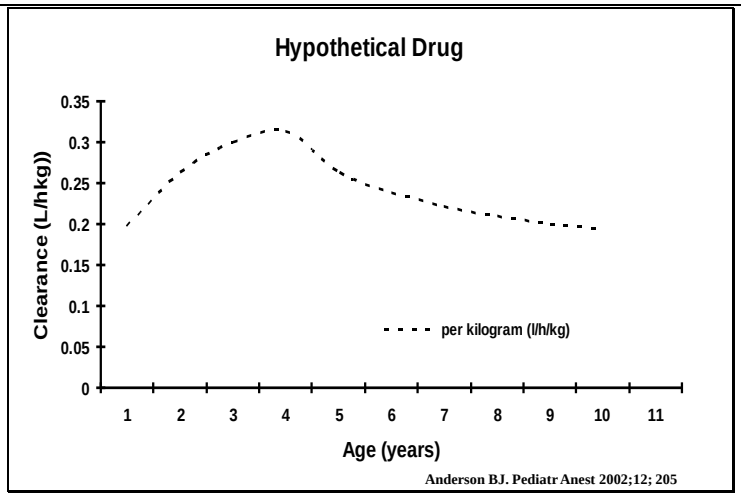
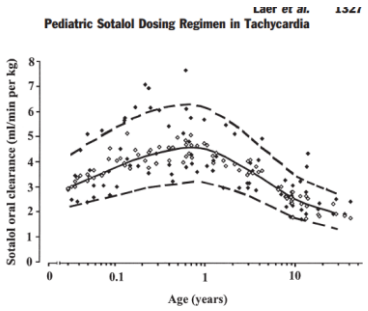


Anderson BJ. Pediatr Anest 2002;12; 205

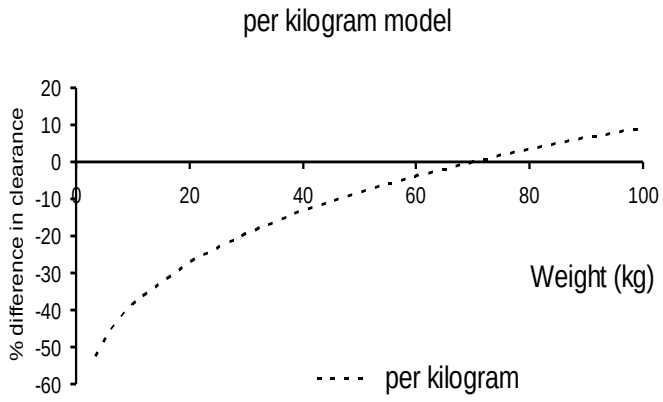
Slide 22

Sotolol clearance changes with age



Laer S. J Am Coll Cardiol 46:1322-30

Slide 23



Holford N. Clin Pharmacokinet 1996;30:329

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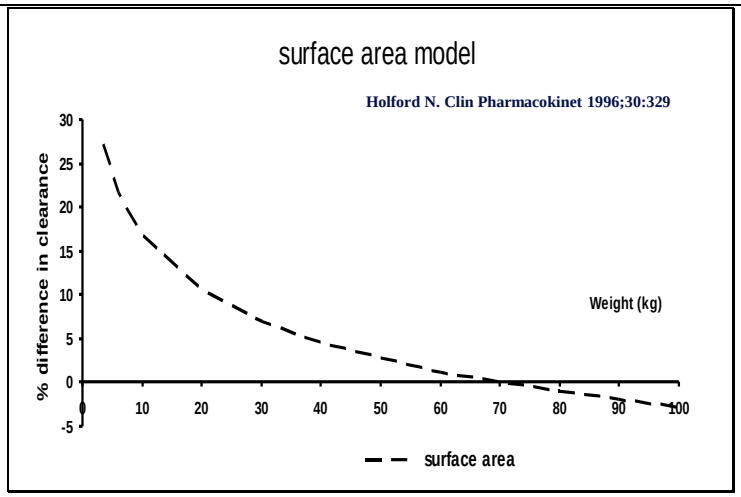
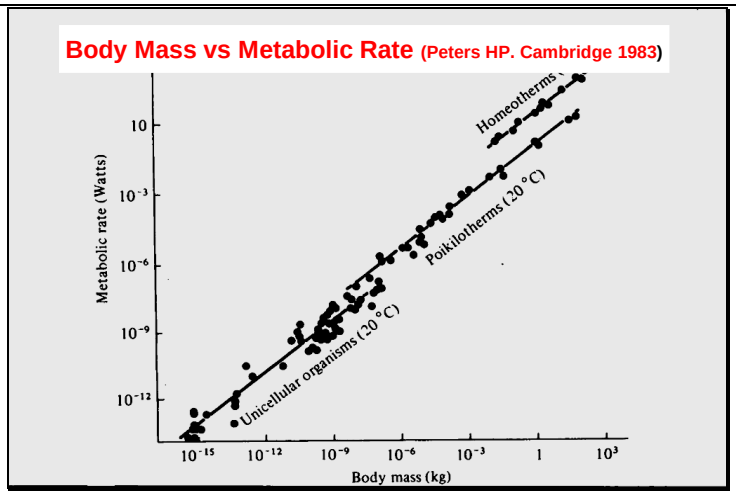
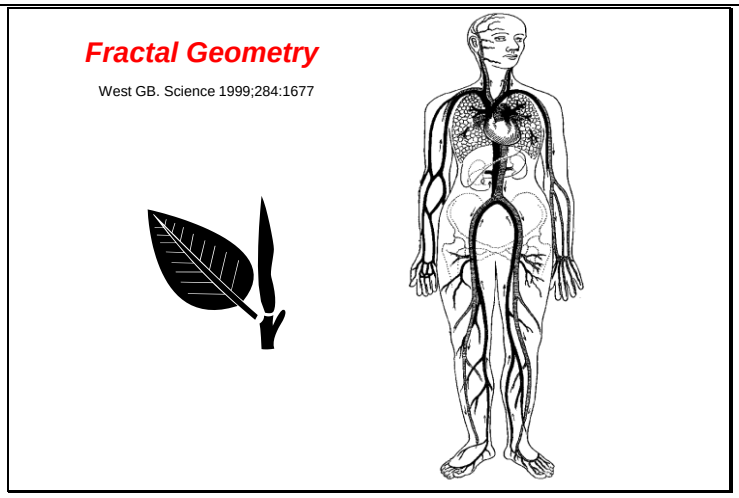
Body Surface Area Model

- **Nomogram required**
  - **BSA = $W(kg)^{0.425} * H(cm)^{0.725} * 0.007184$**
- **Original model from only 9 individuals**
  - **Du Bois D. Arch Intern Med 1916;17:863**
- **Works reasonably well 7-100 kg**
  - **Can be estimated using $Wt^{2/3}$**

Slide 25		
Slide 26		
Slide 27		

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Allometric Theory

$$CL = CL_{std} * (WT / WT_{std})^{3/4}$$

$$V = V_{std} * (WT / WT_{std})^{1}$$

$$T = T_{std} * (WT / WT_{std})^{1/4}$$

West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9.

NOTE Surface area model can be approximated by exponent of 2/3

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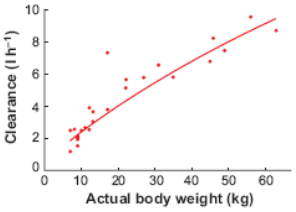
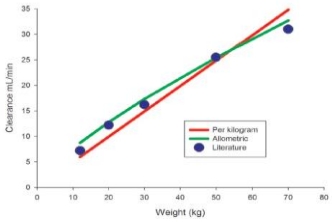
Allometric Examples



Booth BP, Rahman A, Dagher R, Griebel D, Lennon S, Fuller D, et al. Population pharmacokinetic-based dosing of intravenous busulfan in pediatric patients. J Clin Pharmacol. 2007;47(1):101-11.



Drover D, Hammer G, Anderson BJ. The pharmacokinetics of ketorolac after single postoperative intrnasal administration is adolescent patients. Analg Anesth 2011: 114 (6): 1270-6

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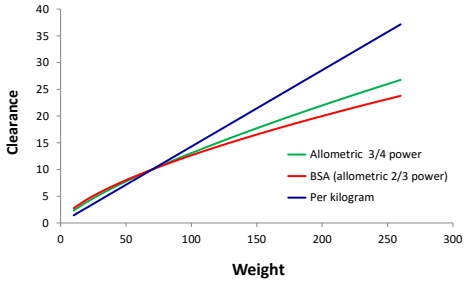
Clearance changes with weight



Anderson BJ. Pediatric Anesthesia. 2017;1–9.

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PAEDIATRIC DOSING

Term	3.5 kg	12%
3 mo	6.0 kg	15%
6 mo	7.5 kg	20%
1 yr	10 kg	25%
3 yr	14 kg	33%
7 yr	22 kg	50%
10 yr	30 kg	60%

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CLEARANCE: A Mechanism Based Model

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF \cdot OF$$

Size

Maturation

Organ Function

CL_{GRP}=Group clearance CL_{STD}=Population standard clearance

WT =Total Body Weight WT_{STD}=Standard weight e.g. 70 kg

Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.

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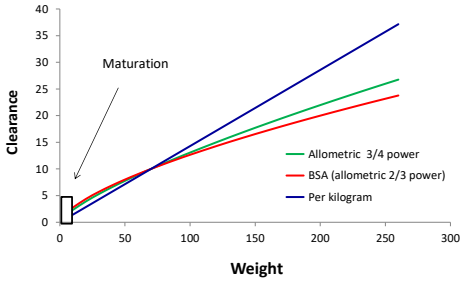
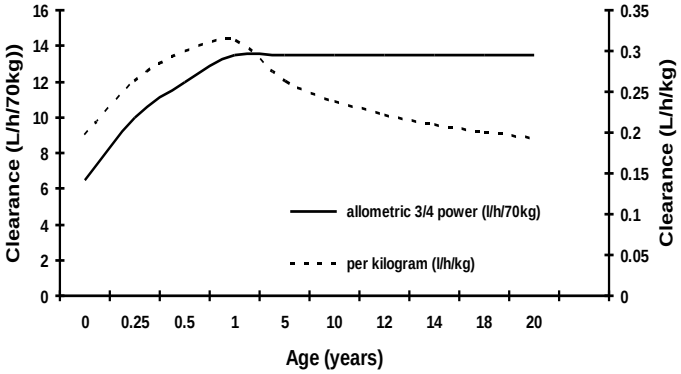
Table 3 Examples that support the proposal that CL scales allometrically within humans

Drug	N	Age	Weight (kg)	Allometric coefficient	95% confidence interval	CV	Reference
Propofol	270	2–88 years	Range 12–100	0.76			(66)
Propofol	22	3–17 months	Range 8.3–12.5	0.61	0.38, 0.84	19.7%	(150)
Busulfan	24	3 months–16 years	Mean 23.8 Range 7.1–62.6	0.74	0.59, 0.90	10.7%	(45)
Phenytoin	322	18.4 SD 17.3 years 3 data sets (*a*) 29.5 SD 15.2 years (*b*) 6.05 SD 3.95 years (*c*) 1.33 SD 0.62 years	(*a*) 54.4 SD 16.7 (*b*) 22.9 SD 11.6 (*c*) 11.8 SD 2.07	0.63	0.58, 0.67	3.7%	(63)
Oxycodone	39	6 months–7 years	Mean 16.3 Range 8–43	0.87	0.64, 1.10	13.3%	(151)
Pyrimethamine	89	1 week–14 years	Range 3–59	0.53	0.47, 0.59	5.8%	(34)
Sulfadoxine	89	1 week–14 years	Range 3–59	0.64	0.58, 0.70	4.8%	(34)
Methotrexate	49	6 months–17 years	Mean 30.56 Range 7.46–80	0.88			(152)
Valproate	225	0.1–14 years	Mean 31.3 Range 4–74	0.72	0.66, 0.77	4.2%	(153)
Sotolol	76	0.03–17 years	Mean 16 (SD 17.1)	0.58	0.42, 0.74	14.4%	(154)

Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. Annu Rev Pharmacol Toxico 2008.

Slide 34	**Maintenance Dose in Child** $CL_{CHILD} = CL_{ADULT} \times \left(\frac{weight_{CHILD}}{weight_{ADULT}}\right)^{3/4}$	
Slide 35	**Clearance changes with weight** 	
Slide 36	**Hypothetical Drug**  Anderson BJ. Pediatr Anest 2002;12; 205	

Slide 37

Age and Maturation

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF \cdot OF$$

Size

Maturation

Organ Function

CL_{GRP}=Group clearance CL_{STD}=Population standard clearance

WT =Total Body Weight WT_{STD}=Standard weight e.g. 70 kg

Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.

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How to Describe Clearance Maturation?

- **Theory**
  - **Should be close to zero at conception**
    - **CL will appear during development in utero**
  - **Should reach adult values around age 20**
- **Observations**
  - **Slow changes after premature birth**
  - **Rapid changes around time of normal gestation**
  - **Slow change in older children**

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Which Age?

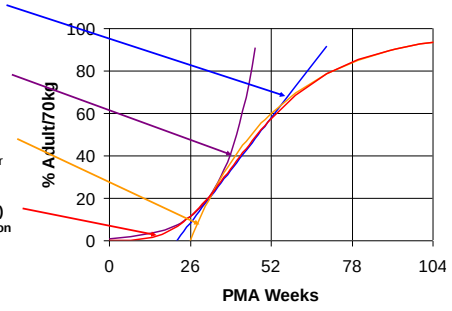
- Post-natal age (PNA)
  - Does not account for *in utero* maturation
- Post-menstrual age (PMA)
  - On average 2 weeks longer than biological age
- Post-conception age (PCA)
  - The biological age but not widely recorded

Slide 40

Maturation Models

- Linear increase (Linvall & Reith 2005)
  - OK for small age ranges e.g. premature neonates
- Exponential increase (Anderson 2000)
  - Premature and term OK but not adult values
- Asymptotic Exponential (Hayton 2002)
  - Term and adult OK but too fast for premature neonates
- **Sigmoid Emax (Tod et al. 2001)**
  - **Matches theory and observation across all ages**

$$MF = \frac{PMA^{HillCL}}{PMA^{HillCL} + TM_{50}^{HillCL}}$$



Anderson BJ. Annu. Rev. Pharmacol. Toxicol. 2008. 48:303–32

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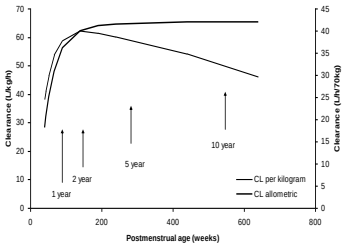
Dexmedetomidine Maturation



- Post-natal age (PNA)
  - Does not account for *in utero* maturation
- Post-conception age (PCA)
  - The biological age but not widely recorded
- Post-menstrual age (PMA)
  - On average 2 weeks longer than biological age

Potts A. Pediatr Anesth 2009

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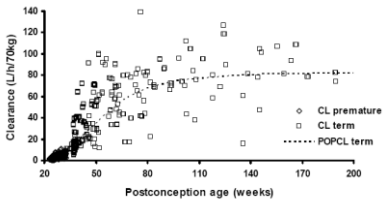
Morphine Clearance



CLmax=84.2 L/h/70kg
TM50=58 weeks PMA
Hill=3.92

449 Preterm
23-32 weeks PMA
184 Infants
0-3 years PNA

Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial. Br J Anaesth 2008;101(5): 680–689.

Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-17.

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Morphine infusion

- target concentration 10 mcg/L

- **Birth** **5 mcg/kg/h**
- **1 Month** **8.5 mcg/kg/h**
- **3 Months** **13.5 mcg/kg/h**
- **1 Year** **18 mcg/kg/h**
- **2 Year** **16 mcg/kg/h**

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Clearance changes with age

Allometric size model

+

Maturation model

Slide 45

ORGAN FUNCTION

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF$$

Size | Maturation | Organ Function

CL_{GRP}=Group clearance CL_{STD}=Population standard clearance

WT =Total Body Weight WT_{STD}=Standard weight e.g. 70 kg

Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.

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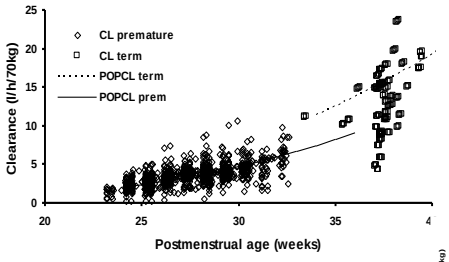
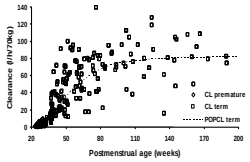
Ventilated premature neonates in NICU have reduced morphine clearance





Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial. Br J Anaesth 2008.(in press)

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A PKPD approach to determine dose

$$TC = \frac{C_{50} \times TE}{E\max - TE}$$ **Equation 1**

$$Size = \left(\frac{WT}{WT_{STD}}\right)^{3/4}$$ **Equation 2**

WT_{STD}=Weight in a standard individual (e.g. 70 kg)

$$Maturation = \frac{PMA^{Hill}}{PMA^{Hill} + TM_{50}^{Hill}}$$ **Equation 3**

Hill=Steepness of the maturation function

$$OrganFunction = \frac{OF_{actual}}{OF_{normal}}$$ **Equation 4**

OF_{actual}=Current organ function in an individual e.g. GFR=3L/h

OF_{normal}=Predicted organ function in a healthy individual e.g. GFR=6 L/h

$$CL = CL_{STD} \times Size \times Maturation \times OrganFunction$$ **Equation 5**

CL_{STD} is the CL in an individual with standard covariates (e.g. WT, GFR)

$$MDR = CL \times TC$$ **Equation 6**

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ALTERED PHARMACOKINETICS

- **Absorption**
- **Metabolism**
- **Volume of distribution**
- **Bioavailability**
- **Protein binding**

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Neonatal Absorption

- **Skin thickness**
- **↑ intragastric pH**
  - **↑ bioavailability acid-labile compounds e.g. Penicillin G**
  - **↓ bioavailability weak acids e.g. pentobarbitone**
- **Delayed gastric emptying**
  - **Tmax delayed**
- **Reduced transport bile salts**
  - **↓ entero-hepatic circulation opioids**

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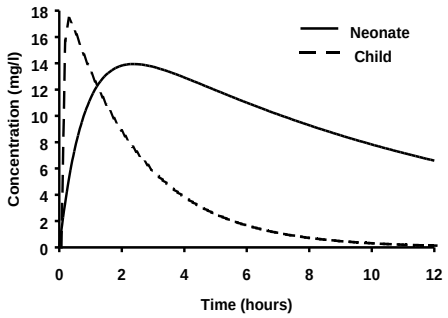
Oral Absorption of Paracetamol



Anderson BJ. Anesthesiology 2002

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Volume of distribution

- **Body composition changes**
- **Vd determines initial plasma concentration (Cp) after an intravenous dose of a drug**

Dose = Cp x Vd

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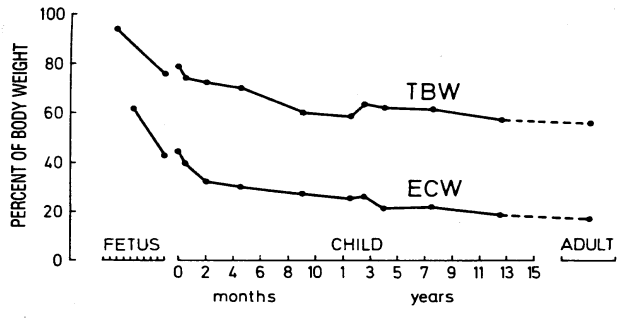
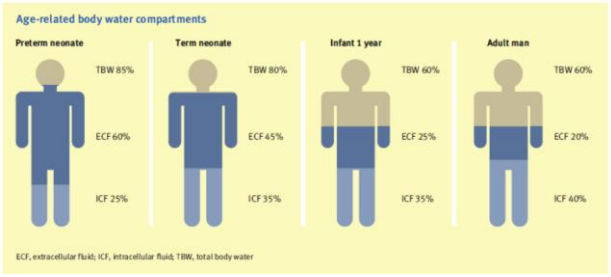
Body Water



Friis-Hansen B. Pediatrics 1971

Slide 53

Body Water



Anderson BJ. AICM 2002

Slide 54

Predicting Vd in infants

- **Morphine - ↓ Vd in neonates**
- **Pethidine - ↑ Vd in neonates**

Vd determined by

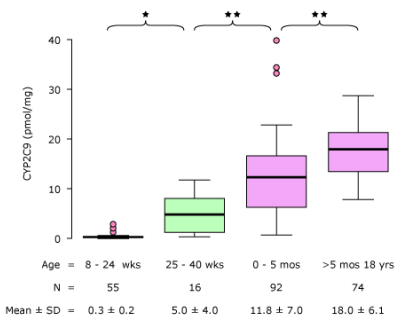
- body composition (muscle bulk, fat content etc)

- drug properties (lipophilicity, protein binding etc)

Slide 55	**Post Natal Drug Disposition** • Volume of Distribution – "Size" predicted by Wt – simple L/kg rule • Water – 'Wet' at birth ECF 50% of Wt – adult 'dry' ECF 25% of Wt within 3 months • Fat – 'Skinny' at birth Fat 10% of Wt – adult Fat 20% of Wt within 3 months	
Slide 56	**Clearance** • **Immature hepatic enzymes** **glucuronide** • **Renal function reduced** **aminoglycosides**	
Slide 57	**CYP Maturation**  • **cytochrome P450** – CYP2E1 surges after birth – CYP2D6 soon thereafter – CYP3A4, 2C 1st week – CYP1A2 last to appear • Normal maturation unknown Kearns GL. N Engl J Med 2003	

Slide 58

CYP2C9 Maturation (Phase I)



Koukouritaki SB. J Pharmacol Exp Ther 2004

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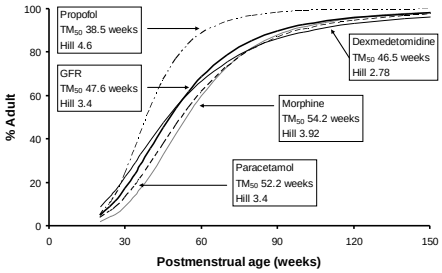
Renal and Metabolic Maturation



Propofol Metabolism
Glucuronide
CYP2B6, CYP2C9 or CYP2A6

Allegaert 2007, Rhodin 2009, Potts 2008, Anand 2008, Anderson 2009

Slide 60

Caffeine - a long acting stimulant in neonates

- **Good central respiratory stimulant**
- **Poor hepatic clearance Immature P450 CYP1A2**
- **Immature renal clearance**
- **T1/2 days in neonate, hours in adults**

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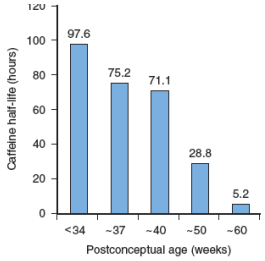


Data from DeCarolis MP, Romagnoli C, Muzil U, et al. Pharmacokinetic aspects of caffeine in premature infants. Dev Pharmacol Ther 1991;16:117-22.

Slide 62

Impact of Gender

- P-glycoprotein expression, CYP3A4
  - Schwartz JB. Clin Pharmacokinet 2003; 42:107-21
  - Cummins CL. Clin Pharmacol Ther 2002; 72:474-89.
- Renal Function (Cockcroft and Gault)
  - Cockcroft DW. Nephron 16:31-41

Slide 63

Post Natal Drug Disposition

- Clearance
  - – 'Size' predicted by Wt3/4
    - Kleiber's law (or BSA)

»Kidney

- – 30% of size predicted value at birth
- – 'Adult' function within 2 years

»Liver

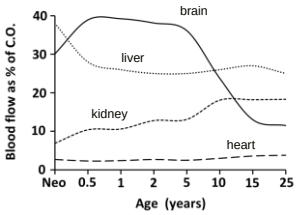
- – 20-50% of size predicted value at birth
- – Adult' function within 1-2 years

Slide 64	***Relative Bioavailability*** **How much drug available?** **Varies with age** • **Skin thickness** • **Gut bacterial colonisation** • **Enzyme pathways** • **Rectal insertion height**	
Slide 65	***The Major PK Covariates in Children*** • **SIZE** • **Maturation** • **Disease** • Drug interactions • Pharmacogenetics • Environmental factors • Circadian rhythms	
Slide 66	***Body Composition*** • Total body water and ECF are increased in neonates • Fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4-5 months of age. • "Baby fat" is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult) • Reduced binding proteins e.g. AAG • Spinal column takes greater proportion body mass	

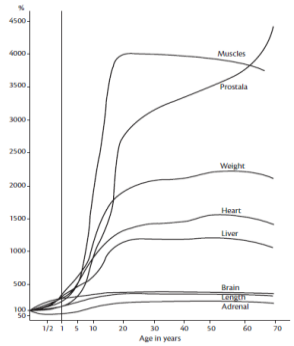
Slide 67

Growth

- organ size
- organ blood flow



Bissonnette B. Pediatric anesthesia: basic principles, state of the art, future. PMPH-USA; 2011. p 356



Friis-Hansen, B. (1971). "Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth." Pediatrics 47(1): Suppl 2:264

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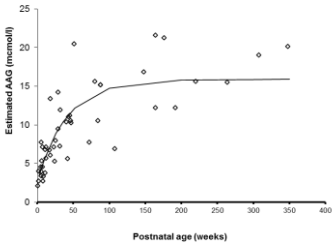
Protein binding - AAG

- Alpha-1 acid glycoprotein reduced in neonates
- Bupivacaine is bound to AAG



Bolus epidural dose of bupivacaine in neonates is lower than in children (1.5-2 mg/kg vs. 2.5 mg/kg) because a greater proportion will be unbound drug and it is unbound drug that exerts effect

Booker P. Br J Anaesth 1996

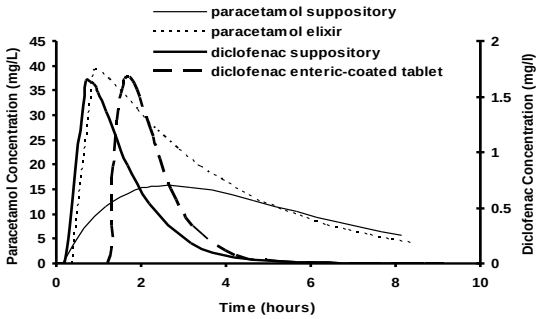
Slide 69

Formulations & Delivery

- **Children prefer liquid formulations**
- **IV may need lots of diluent**
- **Exact dose may be hard to give**
- **Use of IV formulations orally**
- **Taste**

Slide 70

Formulation time-concentration profile



Van der Marel Paediatr Anaesth 2004;14:443-51

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Altered Pharmacodynamics

- **Bronchodilators (sm muscle↓)**
- **Warfarin (sensitivity ↑)**
- **Cyclosporin (immunosuppression ↑)**
- **Midazolam ($GABA_A$ receptor ↑)**
- **Calcium and neonatal heart**
- **Gastric prokinetics (↓ sensitivity)**

Slide 72

Impact Pharmacogenetics

- Limited impact neonates
- Enzyme responsible for ≥ 50% CL
- Steep dose-response curve

  and

  Narrow therapeutic window
- Active metabolite formed by enzyme

Fishbain DA. Pain Med 2004:5:81

- CYP 2C9 & celecoxib
  - Stempak D. Clin Pharmacol Ther 2005

Slide 73	**Drugs in breast milk** **Neonatal concentration** • How much drug in breast milk (milk/plasma) – Diffusion, ion trapping, lipid partition – Maternal concentration • How much breast milk ingested • Bioavailability • Clearance	
Slide 74	**Dosing During Breast Feeding** • 30-60 min after nursing • 3-4 h before next feed	
Slide 75	**Summary** -size important - allometric models satisfactory out of infancy -other covariates contributing to PK variability poorly described -PK maturation over 1st year of life -PD differences poorly described **-More work required before we can predict the correct target concentration**	

Slide 76

Time for an Aphorism Change

~~Children are not Small Adults~~

Adults are BIG Children

Children are OLD Babies

Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.

Slide 77

Determining Clearance in Children

- **Size and Age important covariates**
- **Other Covariates**
  - **disease, drug interaction, PD, pharmacogenetics**

Slide 78

Reading Material

- Anderson BJ, Lerman J, Coté CJ. Pharmacokinetics and Pharmacology of Drugs Used in Children. In A Practice of Anesthesia for Infants and Children (Sixth Edition) 2019; 100-176.
- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349:1157-67.
- Koren G. Chapter 60. Special aspects of perinatal and pediatric pharmacology. In Basic & Clinical Pharmacology ed Katzang BG, Appleton & Lange
- Anderson BJ, Holford NHG. Mechanism based concepts of size and maturity in pharmacokinetics. Annual Review of Pharmacology and Toxicology 2008; 48: 303-32.
- Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 2009; 24 (1): 25-36
- Anderson BJ, Meakin GH. Scaling for size; some implications for paediatric anaesthesia dosing. Paediatr Anaesthesia 2002; 12: 205-219
- Bartelink IH, rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006; 45: 1077-1097